Research

Long-Term Exposure to Ambient Fine Particulate Matter (PM$_{2.5}$) and Lung Function in Children, Adolescents, and Young Adults: A Longitudinal Cohort Study

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BACKGROUND: The association between long-term exposure to ambient fine particulate matter with aerodynamic diameter ≤2.5 μm (PM$_{2.5}$) and lung function in young people remains uncertain, particularly in Asia, where air pollution is generally a serious problem.

OBJECTIVES: This study investigated the association between long-term exposure to ambient PM$_{2.5}$ and lung function in Taiwanese children, adolescents, and young adults.

METHODS: This study comprised 24,544 participants 6–24 years of age, with 33,506 medical observations made between 2000 and 2014. We used a spatiotemporal model to estimate PM$_{2.5}$ concentrations at participants' addresses. Spirometry parameters, i.e., forced vital capacity (FVC), forced expiratory volume in 1 s (FEV$_1$), and maximum midexpiratory flow (MMEF), were determined. A generalized linear mixed model was used to examine the associations between long-term exposure to ambient PM$_{2.5}$ and lung function. The odds ratios (ORs) of poor lung function were also calculated after adjusting for a range of covariates.

RESULTS: Every 10-μg/m^3 increase in the 2-y average PM$_{2.5}$ concentration was associated with decreases of 2.22% [95% confidence interval (CI): −2.60, −1.85], 2.94 (95% CI: −3.36, −2.51), and 2.79% (95% CI: −3.15, −2.41) in the FVC, FEV$_1$, and MMEF, respectively. Furthermore, it was associated with a 20% increase in the prevalence of poor lung function (OR: 1.20; 95% CI: 1.12, 1.29).

CONCLUSIONS: Two-year ambient PM$_{2.5}$ concentrations were inversely associated with lung function and positively associated with the prevalence of poor lung function in children, adolescents, and young adults in Taiwan. https://doi.org/10.1289/EHP5220

Introduction

Air pollution was the fourth-leading risk factor for disability-adjusted life-years lost worldwide in 2016 (Gakidou et al. 2017). Ambient particulate matter (PM) alone contributed to 1.4 million deaths due to respiratory diseases [e.g., lower respiratory infection, chronic obstructive pulmonary disease (COPD)] (Gakidou et al. 2017). Fine PM fine with aerodynamic diameter ≤2.5 μm (PM$_{2.5}$) is among the pollutants most detrimental to lung health. Children, adolescents, and young adults are more susceptible to the adverse effects of air pollution for several reasons, such as their more rapid breathing rate, which generally results in the inhalation of higher doses of pollutants, their prolonged airway and alveolar development, and their immature physiological system (Sly and Flack 2008). Therefore, an improved understanding of the effects of air pollution on lung health in children, adolescents, and young adults is crucial.

Previous studies suggest that both short-term (Ward and Ayres 2004) and long-term (Schultz et al. 2017) exposure to ambient PM$_{2.5}$ may affect lung function in children and adolescents. However, only a few such studies used a cohort design with individual-level exposure assessment, which generally provides stronger and more reliable evidence. Furthermore, most cohort studies were conducted in the Americas (Gauderman et al. 2004, 2015) and Europe (Gehring et al. 2013; Schultz et al. 2016), where the air quality is generally better than in Asian countries. To the best of our knowledge, only two published cohort studies have examined the health effects of PM$_{2.5}$ on lung function in Asia, and both had relatively short follow-up periods (Hwang et al. 2015; Roy et al. 2012). However, more than 90% of air pollution-related deaths occur in Asia and Africa (WHO 2018). We therefore conducted a longitudinal cohort study to investigate the association of long-term exposure to PM$_{2.5}$ with lung function in 24,544 participants (age range: 6 to 24 y) in Taiwan. We additionally determined the associated prevalence of poor lung function.

Methods

Study Design and Participants

The participants were from an ongoing longitudinal cohort in Taiwan. Details of this cohort have been described elsewhere (Guo et al. 2018; Wen et al. 2011). In brief, the MJ Health Management Institution has provided Taiwan residents a standard medical screening program through a paid membership since 1994. Members can also pay for their families to join the program. The parents or guardians of the participants in this study were

encouraged to have their children enrolled in the cohort and undergo the advised medical examinations periodically, including anthropometric measures, spirometric examinations, and blood and urinary tests. A self-administered questionnaire was also used to collect information on demographic and socioeconomic factors, lifestyles, and medical history. Participants younger than 18 received medical examinations accompanied by their parents or guardians and completed the questionnaire together with their parents or guardians.

This cohort is an open (dynamic) cohort with no end date. Each year, $\sim 20,000$ new members are recruited to the cohort in addition to the revisits by existing members. The data have been stored electronically since 1996 and contained ~ 0.59 million Taiwan residents with 1.35 million medical visits as of December 2014. Approximately 43.5% of the participants attended at least two medical visits (a range of 2–28 visits). Each participant (or the parents/guardians of participants younger than 18) provided written informed consent before undergoing medical examinations. The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee provided ethical approval for this study.

We selected 31,383 participants aged 6 to 24 y who joined the program between 2000 and 2014, a period during which $PM_{2.5}$ assessment data are available. Children younger than 6 were excluded because they may have difficulties in reliably performing spirometric tests according to the guidelines (Gehring et al. 2013). The participant selection procedure is shown in Figure S1. We excluded 1,554 participants because of incomplete covariate information and 5,285 with forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratios $\geq 100\%$, which may have been mismeasured due to negligence and/or technical errors (total number excluded = 6,839). Compared with the children, adolescents, and young adults included in the analysis, the 6,839 excluded participants had similar distributions of age (mean: 19.75 vs. 20.39), education (middle school or lower: 16.97% vs. 11.84%), smoking status (never smokers: 87.81% vs. 83.49%), and $PM_{2.5}$ concentration (mean: 25.9 µg/m³ vs. 26.5 µg/m³), but a lower proportion of them were male (39.60% vs. 51.87%).

$PM_{2.5}$ exposure assessment. Details of the $PM_{2.5}$ exposure assessment have been described in our previous publications (Guo et al. 2018; Lin et al. 2015). To estimate ground-level $PM_{2.5}$ concentrations, we developed a spatiotemporal model with a resolution of $1 km^2$ using aerosol optical depth data derived from the Moderate Resolution Imaging Spectroradiometer (MODIS) instruments aboard the Terra and Aqua satellites of the U.S. National Aeronautics and Space Administration). The model was validated by comparing the estimated $PM_{2.5}$ concentrations with monitoring data from more than 70 ground-level air pollution monitoring stations in Taiwan. The Pearson correlation coefficients for the yearly average concentrations ranged from 0.72 to 0.83 (Guo et al. 2018).

The address of each participant was collected during each medical examination to ensure that medical reports could be delivered via mail. We geocoded and matched these addresses with the estimated $PM_{2.5}$ concentrations in the study period of 2000–2014. We calculated the annual average $PM_{2.5}$ concentrations during the calendar year of the medical examination and the previous year. We used the mean of these two averages (i.e., a 2-year average) as an indicator of long-term exposure to ambient $PM_{2.5}$ air pollution.

Outcome Measurements

The health outcomes were lung function (continuous variables) and poor lung function (a binary variable: yes vs. no). Lung function included three parameters: FVC (liters), FEV_1 (liters), and maximum midexpiratory flow (MMEF) (liters per second). To be consistent with previous studies, poor lung function was defined as an FEV_1 <85% of the cohort-specific prediction (Gehring et al. 2013; Moshammer et al. 2006), which was calculated according to the 2012 Global Lung Function Initiative equations after adjusting for sex, age, and height (Quanjer et al. 2012).

Details of the spirometry tests were provided in our previous publication (Guo et al. 2018). These tests were conducted by well-trained professionals who adhered strictly to the guidelines of the American Thoracic Society (ATS) (Miller et al. 2005). While standing, each participant was required to blow at least three times into a CHESTGRAPH HI-701 (Chest M.I.) or Microspiro HI-501 device (Chest M.I.). At least two of the three blows were expected to yield reproducible FVC and FEV_1 values (i.e., within 5%). The FVC and FEV_1 values were derived from the largest curve, while the MMEF value was derived from the curve with the largest sum of the FVC and FEV_1. Quality control measures included the documentation of repairs or alternations of spirometers and changes or updates to software according to the ATS guidelines.

Covariates

The medical examinations and quality control practices are described in detail in our previous reports (Chang et al. 2016; Guo et al. 2018; Zhang et al. 2018). We collected demographic, lifestyle, and medical history information using a standard self-administered questionnaire. Height and weight were measured while the participants wore light clothing without shoes. Blood pressure was measured using an auto-sphygmomanometer (CH-5000; Citizen) while the participants were seated. Fasting blood samples were collected in the morning and subjected to lipid profile and plasma glucose analyses using an automatic biochemical analyzer (Hitachi 7150; Hitachi).

Covariates were selected *a priori*, mainly based on literature reviews (Guo et al. 2018; Schultz et al. 2012). The following covariates included age (years), sex (male or female), height (centimeters), weight (kilograms), education (primary school or lower, middle school, high school, college, or higher), smoking status [never, former (smoked at least once but quit later) or current (>1 time/wk)], alcohol drinking [seldom (<1 time/wk), occasional (1–2 times/wk), or regular (≥3 times/wk)], physical activity [inactive, light (e.g., normal walking), moderate (e.g., normal swimming), high, or vigorous (e.g., running)], vegetable and fruit intake [seldom (<1 serving/d), moderate (1–2 servings/d), or frequent (>2 servings/d)], calendar year, and season (spring: March to May; summer: June to August; autumn: September to November; winter: December to February). For longitudinal analyses, time-varying covariates were used, while covariates at baseline were used for cross-sectional analyses.

Statistical Analysis

We used a generalized linear mixed model to investigate the associations between long-term exposure to $PM_{2.5}$ and lung function parameters in the participants. This model included both cross-sectional (baseline data) and longitudinal (both baseline and repeated follow-up data) analyses. For the cross-sectional analysis, only the covariate values at baseline were included in the models, while for the longitudinal analyses, time-varying covariates were used. To ensure a normal distribution, we logarithmically transformed the lung function, age, height, and weight data (Gehring et al. 2013). We also added a city-level random intercept to the cross-sectional analysis to control for within-city clustering effects based on the participants' addresses. Sixteen municipalities or cities were included: Taipei, Keelung, Taoyuan,

Hsinchu, Ilan, Miaoli, Taichung, Changhua, Nantou, Hualien, Yunlin, Chiayi, Tainan, Kaohsiung, Taitung, and Pingtung. Additionally, we included a person-level random intercept in the longitudinal data analysis to account for the effects of repeated measurements. The following two models were used to control for potential effects of the aforementioned covariates: Model 1, which was adjusted for age, sex, height, and weight, and Model 2, which was further adjusted for education, lifestyle factors (i.e., smoking status, alcohol drinking, physical activity, vegetable intake, and fruit intake), season, and calendar year. The effect estimates for every 10-μg/m^3 increase in PM$_{2.5}$ are presented as percent differences in lung function with 95% confidence intervals (CIs). We further conducted an analysis based on PM$_{2.5}$ quartiles, using the lowest quartile as the reference.

We performed a longitudinal data analysis using a logistic random-effect model with person- and city-level random intercepts to estimate associations between 2-y average PM$_{2.5}$ concentrations and the prevalence of poor lung function. The two abovementioned models were used similarly with different covariate combinations. The results are presented as odds ratios (ORs) with 95% CIs.

Additionally, we used the natural cubic spline function with two degrees of freedom to draw the concentration–response curves for an analysis of the concentration–response relationship between PM$_{2.5}$ and lung function and the prevalence of poor lung function. All concentration–response curves were depicted based on longitudinal analyses with full adjustment for Model 2 covariates.

Although it is known that the parents paid for their children to join the medical screening program, information on parent–child relationships was not collected. Thus, parental data (including education level and smoking status) were unavailable for this study. To determine whether associations between PM$_{2.5}$ exposures and lung function might be biased due to uncontrolled confounding by smoking and education, we estimated associations between these factors and PM$_{2.5}$ in adult members of the cohort who were potential parents (based on ages 26–59 y), consistent with the approach used by Di et al. (2017). Specifically, we used separate linear mixed models with individual- and city-level random intercepts to estimate associations of PM$_{2.5}$ (as the dependent variable) with parental smoking status (smoker or nonsmoker) or education (university or lower vs. higher than university), adjusted for the other Model 2 covariates. According to this approach, potential bias due to uncontrolled confounding by these factors would be limited if they are not strong predictors for PM$_{2.5}$ exposure (Di et al. 2017).

We performed subgroup analyses stratified by sex (male vs. female), body mass index (BMI) (<23 vs. ≥23 kg/m^2) and physical activity (inactive or light vs. moderate or high) to control for potential modifying effects. We also conducted the following sensitivity analyses: a) the possibility of significantly different associations was investigated in adolescents [age 11–19 y (WHO 2013)]; b) the possibility of significantly different associations was investigated in young adults [age 20–24 y (Gore et al. 2011)]; c) the annual PM$_{2.5}$ exposure at the year of medical examination was used to assess the stability of PM$_{2.5}$ effects; d) the confounding effects of cigarette smoking were minimized by excluding former and current smokers; e) participants who changed their addresses during the study period were excluded to avoid potential bias; f) participants who provided company addresses were excluded to avoid potential misclassification by different types of address; g) an analysis was conducted by including only participants who underwent repeated medical examinations to assess potentially significant differences between the participants with single vs. repeated measurements; h) an analysis excluding observations with an FEV$_1$/FVC ratio ≥95% was conducted to investigate further effect estimate bias attributable to potential technical error; i) an analysis excluding

participants with self-reported, physician-diagnosed asthma was conducted to eliminate the potential effects of asthma on lung function; and j) the associations between PM$_{2.5}$ and yearly growth of lung function were analyzed.

All statistical analyses were performed using R software (version 3.4.0; R Development Core Team). An association was considered statistically significant with a two-tailed p-value of <0.05.

Results

The data analysis included 24,544 participants, with a total of 33,506 observations. Of the participants, 5,257 (21.4%) had undergone at least two medical examinations (mean number of medical examinations: 1.4; range: 1 to 11). The median visit interval was 21 months [interquartile range (IQR): 13–34 months]. Table 1 presents summary data for the characteristics of individual participants at baseline and averaged across all observations. The participants had a mean age of 20.31 y at baseline, and approximately half (49.70%) were male. The 2-y average PM$_{2.5}$ concentrations were 26.4 μg/m^3 at baseline and 26.5 μg/m^3 for all observations. Figure 1 presents the distribution of PM$_{2.5}$ concentrations by year. A large contrast in PM$_{2.5}$ exposure was observed.

We found significant associations between long-term exposure to ambient PM$_{2.5}$ and lung function parameters. At baseline,

Table 1. Characteristics of the participating children, adolescents, and young adults.

Characteristics	Baseline (n = 24,544)[a]	All observations (n = 33,506)[b]
Age (y)	20.31 ± 3.43	20.39 ± 3.28
Male [n (%)]	12,199 (49.70)	17,381 (51.87)
Education [n (%)]		
Primary school or lower	339 (1.38)	356 (1.06)
Middle school	3,107 (12.66)	3,611 (10.78)
High school	7,304 (29.76)	9,643 (28.78)
College or higher	13,794 (56.20)	19,896 (59.38)
Smoking status [n (%)]		
Never	20,232 (82.43)	27,975 (83.49)
Former	656 (2.67)	841 (2.51)
Current	3,656 (14.90)	4,690 (14.00)
Alcohol consumption [n (%)]		
Never/seldom	23,037 (93.86)	31,455 (93.88)
Former	1,167 (4.75)	1,602 (4.78)
Current	340 (1.39)	449 (1.34)
Physical activity [n (%)]		
Inactive	3,988 (16.25)	4,564 (13.62)
Light	8,368 (34.09)	12,011 (35.85)
Moderate	9,701 (39.52)	13,506 (40.31)
High	2,487 (10.13)	3,425 (10.22)
Vegetable intake [n (%)]		
Seldom	3,605 (14.69)	4,536 (13.54)
Moderate	13,160 (53.62)	17,745 (52.96)
Frequent	7,779 (31.69)	11,225 (33.50)
Fruit intake [n (%)]		
Seldom	10,010 (40.78)	13,319 (39.75)
Moderate	11,408 (46.48)	15,794 (47.14)
Frequent	3,126 (12.74)	4,393 (13.11)
Height (cm)	165.59 ± 8.66	166.16 ± 8.69
Weight (kg)	59.06 ± 13.80	59.91 ± 14.04
FVC (L)	3.21 ± 0.81	3.28 ± 0.83
FEV$_1$ (L)	2.92 ± 0.73	2.99 ± 0.75
MMEF (L/s)	3.60 ± 1.06	3.68 ± 1.08
PM$_{2.5}$ (μg/m^3)[c]	26.4 ± 7.86	26.5 ± 7.82

Note: Statistical data are shown as mean ± standard deviations for continuous variables and counts (percentages) for categorical variables. Data are complete for all variables. FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximum midexpiratory flow; PM$_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm.
[a]Characteristics of the 24,544 children, adolescents, and young adults at baseline.
[b]Characteristics of the 33,506 observations from the 24,544 children, adolescents, and young adults.
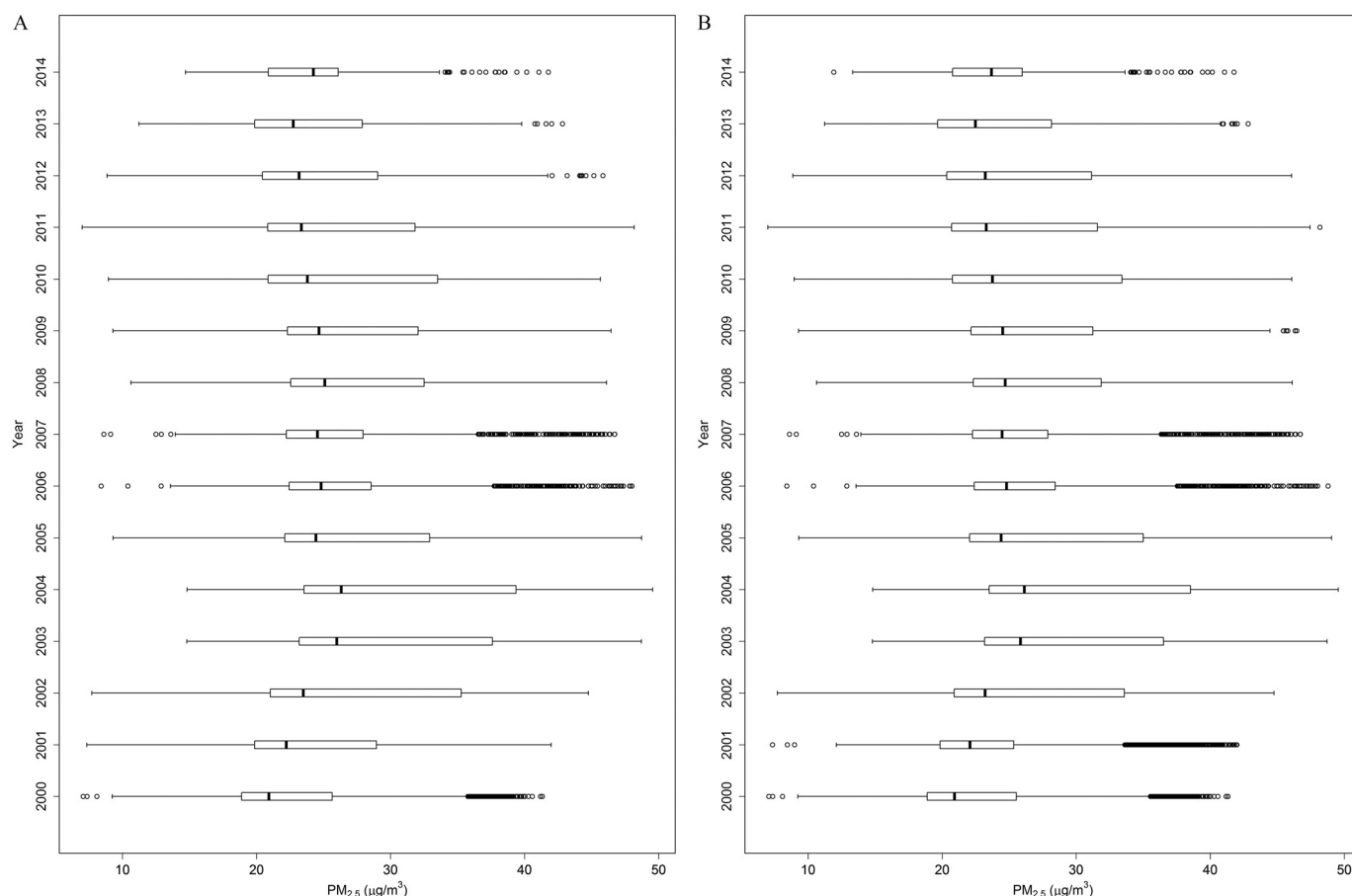[c]The 2-y average PM$_{2.5}$ level of the year of health examination and the previous year.

Figure 1. Box plots of particulate matter with aerodynamic diameter $\leq 2.5 \mu m$ ($PM_{2.5}$) concentration by year in Taiwan. (A,B) Distributions of the 2-y average $PM_{2.5}$ concentrations (the year of health examination and the previous year) by year. Boxes cover the 25th–75th percentiles [interquartile range (IQR)], with center lines indicating the median concentration. Whiskers extend to the highest observations within three IQRs of the box, with more extreme observations shown as circles. (A) Shows the distribution of 24,544 participants at baseline. (B) Indicates the distribution of 33,506 observations from the 24,544 participants.

each 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with decreases of 1.67% (95% CI: −2.15, −1.19), 1.86% (95% CI: −2.33, −1.38), and 2.36% (95% CI: −2.95, −1.75) in the FVC, FEV_1, and MMEF, respectively, after adjusting for covariates (Table 2). The longitudinal data analysis yielded similar associations (Table 2) such that each 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with decreases of 2.22% (95% CI: −2.60, −1.85), 2.94% (95% CI: −3.36, −2.51), and 2.79% (95% CI: −3.15, −2.41) in the FVC, FEV_1, and MMEF, respectively.

A 10-$\mu g/m^3$ increase in 2-y average $PM_{2.5}$ was also associated with poor lung function (adjusted OR = 1.20; 95% CI: 1.12, 1.29) (Table 3). Compared with participants in the first quartile of $PM_{2.5}$ exposure, those in the second, third, and fourth quartiles had ORs of 1.14 (95% CI: 1.05, 1.24), 1.13 (95% CI: 1.03, 1.23), and 1.14 (95% CI: 0.95, 1.36) for poor lung function, respectively.

The longitudinal concentration–response curves further indicated that the associations of $PM_{2.5}$ with the lung function parameters FVC, FEV_1, and MMEF were generally nonlinear (chi-square values are 36.3, 30.2, and 60.7, respectively, with all p-values <0.001), after adjusting for Model 2 covariates (Figure 2A–C). Lung function seemed to decrease slightly more sharply up to a $PM_{2.5}$ concentration range of 20–25 $\mu g/m^3$ and seemed to decrease slightly more slowly thereafter. We also observed a similar inflection point of 20–25 $\mu g/m^3$ for the association between $PM_{2.5}$ and the prevalence of poor lung function, although the associations were generally linear (chi-square = 2.7; p = 0.26), after adjusting for the Model 2 covariates (Figure 2D).

Smoking and education were associated with small differences in average $PM_{2.5}$ concentrations among parents enrolled in the medical screening program: 0.02 $\mu g/m^3$ lower (95% CI: −0.04, 0.00) for smokers compared with nonsmokers, and 0.03 $\mu g/m^3$ higher (95% CI: 0.00, 0.06) for parents with a university education or lower vs. more than a university education. These estimates suggest that smoking and education were unlikely to be strong confounders of associations between $PM_{2.5}$ and lung function in our study population.

The subgroup analyses regarding modifying effects are presented in Table S1. We observed statistically significant modifying effects of BMI on lung function. By contrast, we generally did not observe significant modifying effects of sex (except for FEV_1) and physical activity. No statistically significant modifying effects were observed for poor lung function (p-values ranged from 0.06 to 0.47).

The results of the sensitivity analyses are presented in Tables S2–S4. Associations with the lung function measures were generally consistent between adolescents (ages 11–19 y; 8,537 participants with 11,480 observations) and young adults (ages 20–24 y; 18,186 participants with 22,000 observations) but with minor differences in exposure quartiles (Table S2). ORs for poor lung function were consistent between the two age groups with the exception of ORs comparing the fourth with the first quartiles of exposure (OR = 0.90; 95% CI: 0.67, 1.22 and OR = 1.40; 95% CI: 1.16, 1.69 for children and adolescents, as well as young adults, respectively) (Table S2). Inverse associations with the

Table 2. Associations between $PM_{2.5}$ exposure and lung function parameters in children, adolescents, and young adults.

Models[a]	Model 1 Difference [% (95% CI)]	p-Value	Model 2 Difference [% (95% CI)]	p-Value
Baseline data (n = 24,544)				
FVC				
Second quartile[b]	−0.38 (−0.91, 0.14)	0.16	−1.40 (−1.91, −0.90)	<0.01
Third quartile[b]	−0.57 (−1.12, −0.02)	0.04	−2.24 (−2.76, −1.71)	<0.01
Fourth quartile[b]	−2.68 (−3.73, −1.62)	<0.01	−2.35 (−3.39, −1.30)	<0.01
Every $10\,\mu g/m^3$	−1.39 (−1.87, −0.91)	<0.01	−1.67 (−2.15, −1.19)	<0.01
FEV_1				
Second quartile[b]	−0.78 (−1.31, −0.24)	<0.01	−1.68 (−2.20, −1.16)	<0.01
Third quartile[b]	−0.63 (−1.19, −0.07)	0.03	−2.13 (−2.67, −1.59)	<0.01
Fourth quartile[b]	−2.67 (−3.73, −1.59)	<0.01	−2.42 (−3.48, −1.34)	<0.01
Every $10\,\mu g/m^3$	−1.61 (−2.09, −1.12)	<0.01	−1.86 (−2.33, −1.38)	<0.01
MMEF				
Second quartile[b]	−1.34 (−2.18, −0.50)	<0.01	−2.00 (−2.83, −1.17)	<0.01
Third quartile[b]	−1.55 (−2.41, −0.68)	<0.01	−2.68 (−3.53, −1.81)	<0.01
Fourth quartile[b]	−3.07 (−4.54, −1.59)	<0.01	−3.08 (−4.46, −1.69)	<0.01
Every $10\,\mu g/m^3$	−2.23 (−2.86, −1.58)	<0.01	−2.36 (−2.95, −1.75)	<0.01
Longitudinal data (n = 33,506)				
FVC				
Second quartile[c]	−2.75 (−3.13, −2.38)	<0.01	−2.18 (−2.55, −1.81)	<0.01
Third quartile[c]	−3.05 (−3.50, −2.60)	<0.01	−2.60 (−3.03, −2.15)	<0.01
Fourth quartile[c]	−5.04 (−5.88, −4.19)	<0.01	−3.19 (−4.03, −2.33)	<0.01
Every $10\,\mu g/m^3$	−2.73 (−3.14, −2.32)	<0.01	−2.22 (−2.60, −1.85)	<0.01
FEV_1				
Second quartile[c]	−2.20 (−2.24, −2.17)	<0.01	−2.43 (−2.82, −2.05)	<0.01
Third quartile[c]	−2.71 (−3.08, −2.35)	<0.01	−2.92 (−3.38, −2.46)	<0.01
Fourth quartile[c]	−3.57 (−3.60, −3.53)	<0.01	−2.94 (−3.87, −2.01)	<0.01
Every $10\,\mu g/m^3$	−3.27 (−3.72, −2.83)	<0.01	−2.94 (−3.36, −2.51)	<0.01
MMEF				
Second quartile[c]	−4.02 (−4.60, −3.43)	<0.01	−3.69 (−4.27, −3.10)	<0.01
Third quartile[c]	−4.05 (−4.73, −3.37)	<0.01	−4.15 (−4.82, −3.48)	<0.01
Fourth quartile[c]	−5.20 (−6.01, −4.37)	<0.01	−4.73 (−5.54, −3.91)	<0.01
Every $10\,\mu g/m^3$	−2.81 (−3.21, −2.40)	<0.01	−2.79 (−3.15, −2.41)	<0.01

Note: $PM_{2.5}$ exposure refers to the 2-y average $PM_{2.5}$ concentrations (the year of health examination and the previous year). Data are complete for all variables. CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximum midexpiratory flow; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm.
[a]Generalized linear mixed model with log link function was used. Model 1 was adjusted for age, sex, height, and weight. Model 2: Model 1 plus further adjustments for education, calendar year, season, and lifestyle factors (smoking status, alcohol consumption, physical activity, vegetable intake, and fruit intake).
[b]First quartile of $PM_{2.5}$ ($<21.01\,\mu g/m^3$) is the reference level; the second, third, and fourth quartiles correspond to $21.01–23.69\,\mu g/m^3$, $23.69–30.86\,\mu g/m^3$, and $≥30.86\,\mu g/m^3$, respectively.
[c]First quartile of $PM_{2.5}$ ($<21.15\,\mu g/m^3$) is the reference level; the second, third, and fourth quartiles correspond to $21.15–23.74\,\mu g/m^3$, $23.74–30.35\,\mu g/m^3$, and $≥30.35\,\mu g/m^3$, respectively.

continuous lung function outcomes remained significant and were generally consistent with regard to magnitude when based on the annual $PM_{2.5}$ in the year of the examination (vs. the 2-y average) and, when analyses were restricted to participants who were nonsmokers, did not move during the study period (Table S3), provided a residential (vs. workplace) address, had more than one study examination, had an FEV_1/FVC ratio <95%, and

Table 3. Associations between $PM_{2.5}$ exposure and the prevalence of poor lung function in children, adolescents, and young adults.

Models[a]	Model 1 OR (95% CI)	p-Value	Model 2 OR (95% CI)	p-Value
Second quartile[b]	1.06 (0.98, 1.15)	0.15	1.14 (1.05, 1.24)	<0.01
Third quartile[b]	1.01 (0.93, 1.10)	0.83	1.13 (1.03, 1.23)	<0.01
Fourth quartile[b]	1.19 (1.01, 1.42)	0.04	1.14 (0.95, 1.36)	0.15
Every $10\,\mu g/m^3$	1.16 (1.16, 1.16)	<0.01	1.20 (1.12, 1.29)	<0.01

Note: The effects are presented as odds ratios (ORs) with 95% confidence intervals (CIs). $PM_{2.5}$ exposure refers to 2-y average $PM_{2.5}$ concentrations (the year of health examination and the previous year). Data are complete for all variables. $PM_{2.5}$, fine particulate matter with an aerodynamic diameter ≤2.5 μm.
[a]Generalized linear mixed model with logistic link function was used. Model 1 was adjusted for age, sex, height, and weight. Model 2: Model 1 plus further adjustment for education, calendar year, season, and lifestyle factors (smoking status, alcohol consumption, physical activity, vegetable intake, and fruit intake).
[b]First quartile of $PM_{2.5}$ ($<21.15\,\mu g/m^3$) is the reference level; the second, third, and fourth quartiles correspond to $21.15–23.74\,\mu g/m^3$, $23.74–30.35\,\mu g/m^3$, and $≥30.35\,\mu g/m^3$, respectively.

did not have self-reported, physician-diagnosed asthma (Table S3). Associations with poor lung function were also generally consistent with the primary analysis (Table S3). We also found that every $10\text{-}\mu g/m^3$ increase in $PM_{2.5}$ was associated with a decreased growth of 0.003, 0.008, and 0.014 L/y in FVC, FEV_1, and MMEF, respectively (Table S4).

Discussion

To the best of our knowledge, this is the largest Asian study that investigated the associations of long-term ambient $PM_{2.5}$ exposure with lung function parameters and the prevalence of poor lung function in children, adolescents, and young adults. Our results show consistent associations of long-term $PM_{2.5}$ exposure with decreases in the lung function parameters of FVC, FEV_1, and MMEF. These decreases seemed generally sharper within the lower range of $PM_{2.5}$ air pollution (less than $20–25\,\mu g/m^3$). Long-term exposure to $PM_{2.5}$ was also found to associate with an increased prevalence of poor lung function in the same population. Similarly, the effect on the prevalence of poor lung function seemed stronger within the lower range of $PM_{2.5}$ air pollution (less than $\sim 20–25\,\mu g/m^3$).

$PM_{2.5}$ and Lung Function

Only a few previous studies have examined the effects of exposure to $PM_{2.5}$ on the lung function parameter MMEF. However, MMEF
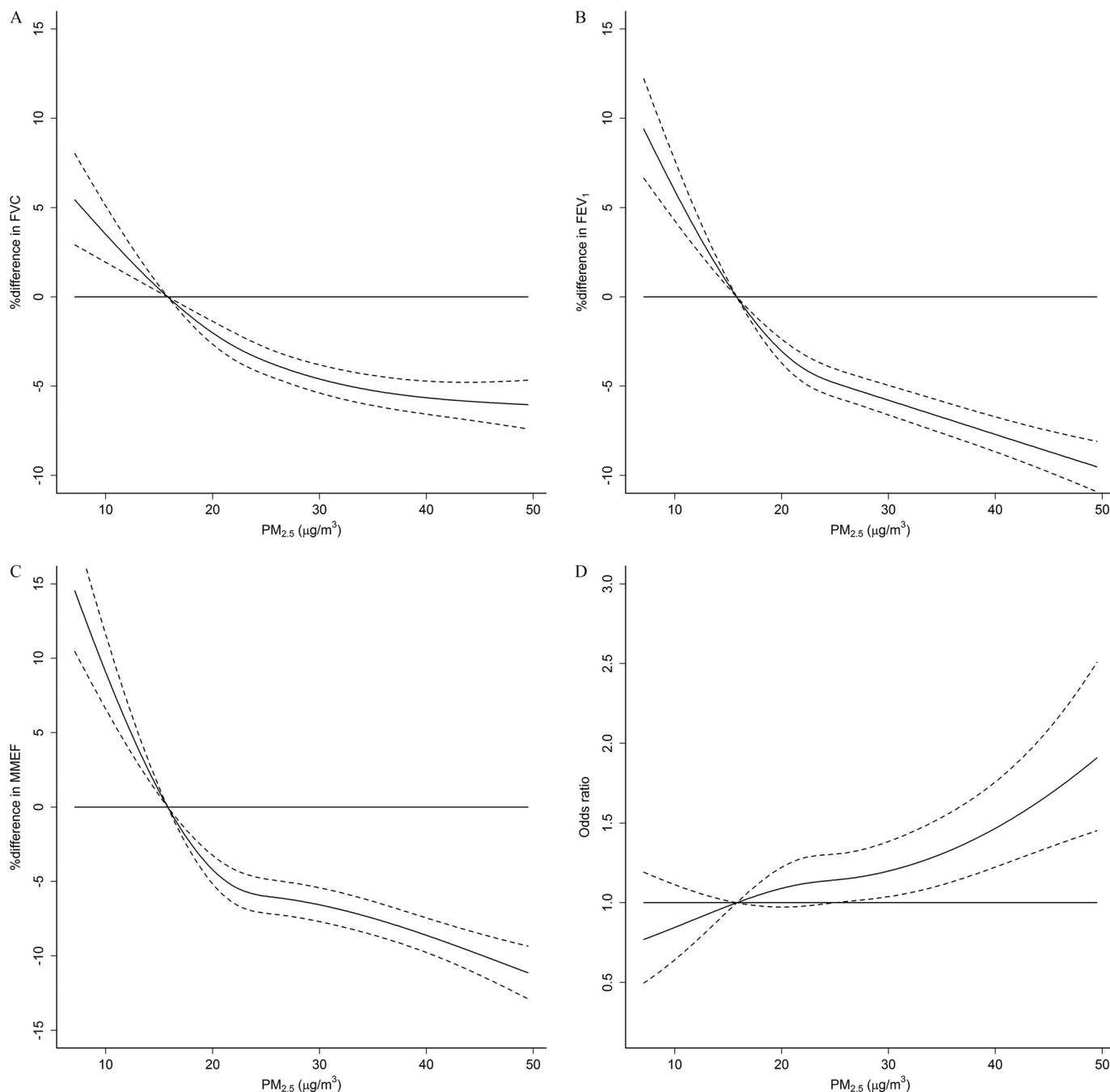
Figure 2. Concentration–response associations between fine particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and lung function in children, adolescents, and young adults. (A–D) Longitudinal associations of $PM_{2.5}$ with forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), maximum midexpiratory flow (MMEF), and the prevalence of poor lung function, respectively. The black solid lines represent the estimated effects on lung function, and the dashed lines refer to the corresponding 95% confidence intervals. Generalized linear mixed model (GLMM) with the log link function was used for FVC, FEV_1, and MMEF, and GLMM with logistic link function was used for the prevalence of poor lung function. All models were adjusted for age, sex, height, weight, education, calendar year, season, and lifestyle factors (smoking status, alcohol consumption, physical activity, vegetable intake, and fruit intake).

is an important indicator of small airway function (Gilliland et al. 2000). In this study, we observed that exposure to ambient $PM_{2.5}$ generally had a stronger association with MMEF than with FVC and FEV_1 [−4.73% (95% CI: −5.54, −3.91) in MMEF vs. −3.19% (95% CI: −4.03, −2.33) in FVC and −2.94% (95% CI: −3.87, −2.01) in FEV_1 for the fourth quartile of $PM_{2.5}$ with reference to the first quartile], consistent with several previous studies (Gauderman et al. 2004; Hwang et al. 2015; Oftedal et al. 2008). This finding suggests that air pollution may have more serious effects on small airway function than on large airway function.

Existing cohort studies provide limited data regarding the effects of long-term exposure to $PM_{2.5}$ on lung function in children and adolescents (Gauderman et al. 2004, 2007, 2015; Gehring et al. 2013; Hwang et al. 2015; Gauderman et al. 2000; Roy et al. 2012). However, our study findings are consistent with some of the few previous studies that are available (Gauderman et al. 2004; Gehring et al. 2013; Hwang et al. 2015). Our estimated effects of ambient $PM_{2.5}$ exposure on FVC and FEV_1 [−2.22% (95% CI: −2.60, −1.85) and 2.94% (95% CI: −3.36, −2.51) per 10-μg/m^3 increase in $PM_{2.5}$] were weaker than those reported by the European Study of Cohorts

for Air Pollution Effects (ESCAPE) [16.88% (95% CI: −36.75, −8.84) for FVC and 4.92% (95% CI: −8.93, −0.72) for FEV_1 for the same $PM_{2.5}$ increment] (Gehring et al. 2013). This discrepancy may be attributable to the higher $PM_{2.5}$ concentrations reported in our study [median (IQR): $23.7\ \mu g/m^3$ (9.2) vs. $9.4\ \mu g/m^3$ (2.6)]. Our results also suggested more rapid decreases in lung function parameters among participants exposed to low $PM_{2.5}$ concentrations compared with those exposed to high concentrations (Figure 2). We speculate that this may be because the participants who were exposed to lower $PM_{2.5}$ concentrations were more sensitive to the effects of $PM_{2.5}$ and these effects were saturated at high $PM_{2.5}$ concentration. However, further studies are warranted to investigate whether there is a clear inflection point at which the effect size changes. In addition, the ESCAPE study focused on children, while our study cohort predominantly comprised adolescents and young adults. Children may be more vulnerable than adolescents/adults to air pollution (Wang et al. 1994). It is difficult to compare our effect magnitudes directly with those of other studies, given the differences in study designs, target participants and pollutants, and statistical methods.

Consistent with our findings regarding lung function parameters, we observed a higher prevalence of poor lung function among participants exposed to higher concentrations of $PM_{2.5}$. Our results are consistent with a study conducted in Boston, United States (Rice et al. 2016). Another three studies of exposure to PM_{10} similarly identified an association with increased prevalence of poor lung function (their ORs ranged from 1.21 to 20.78) (Schultz et al. 2012, 2016; Zeng et al. 2016). By contrast, Janssen et al. (2003) found a nonsignificant inverse association, while Bergstra et al. (2018) found a nonsignificant positive association. This discrepancy might be due to the cross-sectional study design or the relatively short study period.

Effect Modification

We explored several potential modifiers including sex, BMI, and physical activity. Some studies have reported evidence suggesting that males were more sensitive to air pollution (Gauderman et al. 2007, 2015), while others have reported evidence of greater vulnerability among females (Frye et al. 2003; Oftedal et al. 2008) or no significant difference between males and females (Gehring et al. 2013). We did not observe significant effect modification by sex on associations with FVC, MMEF, or the prevalence of poor lung function, but associations with FVC, FEV_1, and poor lung function were stronger for males than females (*p*-interactions are 0.21, 0.01, and 0.06, respectively) (Table S1). Although we observed significant differences in associations between $PM_{2.5}$ and lung function according to BMI, the differences were inconsistent, such that the association with FEV_1 was stronger for participants with BMI $<23\ kg/m^2$, while associations with FVC and MMEF were stronger among those with BMI $\geq 23\ kg/m^2$ (Table S1). Previous studies have also reported inconsistencies regarding the modifying effects of BMI. Rosenlund et al. (2009) showed a weaker association between FEV_1 and air pollution among people with a low–normal BMI, while Siddique et al. (2010) reported stronger associations between air pollution and lung function among both underweight and obese participants compared with those of normal weight, suggesting that the modification effects of BMI might be nonlinear. Associations were not significantly modified by physical activity in this study. In summary, there is limited information on the modifying effects of these factors, and the results from previous studies have been inconsistent. Further studies are warranted.

Potential Mechanism

The biological mechanism underlying the associations between air pollution and lung function parameters is unclear. Previous studies have hypothesized the involvement of pulmonary inflammation (Ghio et al. 2000) or elevated oxidative stress (Hatzis et al. 2006). Animal studies have shown that $PM_{2.5}$ can induce oxidative stress, inflammation, and pulmonary impairment via the generation of free radicals and consumption of antioxidants and related enzymes (Riva et al. 2011). Antioxidant supplementation may protect people from the deleterious effects of air pollution on lung function (Salvi 2007).

Strengths and Limitations

This study has several important strengths. First, it targeted a vulnerable population (children, adolescents, and young adults) with a large sample (24,544 participants with 33,506 observations) in an area with relatively high $PM_{2.5}$ concentration. Additionally, the large sample size enabled us to obtain more stable and precise estimates and provided sufficient power to conduct a series of subgroup and sensitivity analyses. Repeated measurements were available for some of the participants, which enabled a longitudinal analysis. Second, this study developed a novel satellite-based model to estimate long-term exposure to ambient $PM_{2.5}$ at a high spatial resolution ($1\ km^2$). This model enabled an analysis of individual-level exposure and overcame the issue of spatial coverage associated with the use of data collected solely from monitoring stations. Furthermore, the use of satellite data enabled us to track changes in $PM_{2.5}$ exposure over time and account for the effects of such changes on lung health. Finally, the data were collected through a standard medical screening program (Wu et al. 2017). This may minimize investigator bias.

This study has several limitations. First, information about gaseous air pollutants, including SO_2, NO_2, and ozone, was not available. Therefore, we could not distinguish between associations due to $PM_{2.5}$ specifically vs. one or more correlated pollutants or the joint effects of a mixture of pollutants. Second, we did not consider household air pollution because this information was unavailable. Although previous studies have reported strong correlations between indoor and outdoor air pollution, we could not exclude the possible influence of factors that might affect indoor PM concentrations, such as the type of cooking fuel used and the characteristics of home ventilation. Third, data on parental factors that might have confounded associations, including smoking and education, were unavailable. We therefore conducted an additional analysis of associations between these factors and $PM_{2.5}$ exposures among adult program members who were identified as potential parents based on age. The weak associations between these factors and average $PM_{2.5}$ concentrations suggest that parental smoking and education were unlikely to be important confounders, although residual confounding by these and other factors cannot be ruled out. Moreover, associations were generally consistent when limited to nonsmokers, children who did not move during the study period, and those who provided a residential address, had >1 study examination, had FEV_1/FVC ratios <95%, and who did not self-report physician-diagnosed asthma. Fourth, participants were recruited from a voluntary program that required paid membership; thus, children and parents were more educated and had a higher socioeconomic status than the population of Taiwan as a whole, and the findings may not be generalizable to other populations. Fifth, we classified children as having poor lung function based on FEV_1 <85% of the predicted value and did not administer a bronchodilator to further distinguish between reversible obstruction (consistent with asthma) and irreversible obstruction (consistent with COPD, which would be uncommon in our young study population.) However, associations between $PM_{2.5}$ and lung function tests and poor lung function were similar when the analysis was restricted to children without a self-reported diagnosis of asthma. Finally,

we excluded 5,285 (16.8%) participants with an FEV_1/FVC ratio $\geq 100\%$, which may have been mismeasured due to negligence and/or technical error. It is difficult to perform spirometry in large-scale studies, especially in children and adolescents, and many factors might have contributed to these unsuccessful tests, such as participant cooperation and technician skill. However, we collected the data from a standard and routine medical screening program (Wu et al. 2017), and there is no evidence showing that participants with an unsuccessful spirometry are more likely to be associated with $PM_{2.5}$ exposure. Thus, the exclusion is unlikely to have yielded any bias.

In conclusion, long-term exposure to ambient $PM_{2.5}$ was associated with reduced lung function parameters (FVC, FEV_1, and MMEF) and a higher prevalence of poor lung function in a cohort of Taiwanese children, adolescents, and young adults with paid memberships in a medical screening program. We also found preliminary evidence of stronger adverse associations with $PM_{2.5}$ concentrations in the lower range of $PM_{2.5}$ exposures (less than $20-25 \mu g/m^3$). Although the average estimated effects would be negligible in a clinical setting, small effects of $PM_{2.5}$ on lung function in early life could have significant impacts on disease burdens in later life, including COPD and premature mortality. Therefore, our findings provide further support for the urgent need to control air pollution to protect the pulmonary health of children, adolescents, and young adults.

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